DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

94381

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

WARNING LETTER

SEP 29 2003

Blair Ford, M.D.
Department of Neurology
The Neurological Institute
Columbia-Presbyterian Medical Center
710 West 168th Street
New York, New York 10032

Dear Dr. Ford:

The purpose of this letter is to inform you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection at your clinical site and to acknowledge your June 1, 2003, letter to FDA. The inspection took place during the period April 21 to May 5, 2003, and was conducted by L. Glenn Massimilla, Pharm.D., an investigator with FDA's New York District Office.

The purpose of the inspection was to determine if your activities as both the sponsor and investigator in the [redacted] conducted under [redacted] complied with applicable FDA regulations. The products used in the study, the [redacted], are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(h).

Our review of the inspection report submitted by the New York District Office revealed violations of the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812- Investigational Device Exemptions and Part 50- Protection of Human Subjects. Dr. Massimilla listed his findings on a Form FDA-483, "Inspectional Observations," and discussed these findings and several other issues with you at the conclusion of the inspection.

The violations noted on the FDA-483, those identified during our subsequent review of the inspection report, and your written response to the inspectional observations are summarized below:

1. Failure to ensure compliance with the conditions of approval imposed by FDA [21 CFR 812.42, 812.46(a), 812.110(b)]

You failed to ensure compliance with the conditions of approval imposed by FDA in that you enrolled more than the [redacted] subjects initially approved by FDA. In your IDE progress report dated

June 15, 2000, which covers the period March 1, 1999, through February 29, 2000, you stated that [redacted] subjects had been enrolled. Based on study records, maximum enrollment was reached on January 20, 2000.

It was further revealed that during the period January 21, 2000, through October 12, 2000, you enrolled and implanted [redacted] additional subjects with the device(s). When FDA became aware that the enrollment limit of [redacted] had been exceeded, the agency informed you in a letter dated July 21, 2000, to immediately suspend all patient enrollments until you had submitted an IDE supplement and received FDA approval for expansion of the investigation. We observed that at least [redacted] subjects were implanted during the time when enrollment should have been suspended. FDA subsequently approved, on October 12, 2000, an increase in enrollment, to a total of [redacted] subjects ([redacted] and [redacted]). However, you again exceeded this limit as a total of [redacted] subjects were enrolled in the study.

2. **Failure to ensure that informed consent documents contained the most current information regarding reasonably foreseeable risks and other required information [21 CFR 50.25(a)(2) and 50.25(a)(5)]**

The IDE progress report covering the period March 1, 2000, through June 30, 2001, referenced "new information about the hazard of [redacted] in patients with implanted [redacted]" You stated that this risk was added to the informed consent form in use and that all previously implanted patients would be informed about the [redacted] risk.

This risk was not evident in the informed consent in effect at that time or in any subsequent version [21 CFR 50.25(a)(2)]. In addition, none of the consent forms used noted the possibility that FDA may inspect the records [21 CFR 50.25(a)(5)].

FDA advised you in an August 30, 2001, letter to revise your informed consent document provided to study subjects and ensure that patients who had already been enrolled were informed of significant adverse events, i.e., two cases of coma due to adverse interaction between [redacted] and [redacted]. It was not until January 30, 2003, that Robert Goodman, M.D., a co-investigator in your study, notified subjects in writing of these risks as well as advising them to avoid MRIs.

Also, Dr. Massimilla reported that you continued to use the IRB-approved consent form after you completed your IDE, thus giving patients the impression that they were part of a clinical trial when, in fact, they were not. You documented in your files that this had been an oversight.

In your written response to the Form FDA 483, you stated that all study subjects were informed and counseled at a scheduled visit about the risk of [redacted] in those implanted with the [redacted] However, it is unclear if this notification was documented in your records.

3. Failure to obtain FDA approval prior to implementing changes in the investigational plan [21 CFR 812.35(a), 812.150(a)(4)]

You deviated from your approved investigational plan in that you did not administer the [redacted] to subjects at baseline. FDA notified you on July 21, 2000, that, because these changes could have affected the scientific soundness of the investigational plan, FDA and IRB approval was required prior to their implementation.

4. Failure to submit timely progress reports to FDA [21 CFR 812.150(b)(5)]

Sponsors are required to submit progress reports to FDA at least yearly [21 CFR 812.150(b)(5)]. Your progress reports, covering the following periods, were submitted late:

March 1, 1999 - February 29, 2000 -- dated June 15, 2000
March 1, 2000 - June 30, 2002 -- report covered 15 months
July 1, 2002 - unspecified end date -- dated November 11, 2002

In response to this observation, you indicated that the annual reports were submitted late because the study was unfunded and it was hard for you to keep up with paperwork.

The violations described above are not intended to be an all-inclusive list of deficiencies found in your study. When conducting clinical investigations of products regulated by FDA, whether acting as a sponsor, an investigator, or both, it is your responsibility to adhere to all applicable federal statutes and regulations.

Within fifteen (15) working days of receipt of this letter, you must provide this office with written documentation of the specific steps you have taken or will be taking to prevent the types of problems described above from recurring in future studies of FDA-regulated products. The failure to respond may result in regulatory action against you without further notice.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Barbara A. Crowl. A copy of this

letter has been sent to FDA's New York District Office, 850 Third Avenue, Brooklyn, New York 11232. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Ms. Crowl at (301) 594-4720, ext. 168.

Sincerely yours,

Michael E Marcinelli

for Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc: Andrew Wit, M.D.
Chair, Institutional Review Board
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